AIDS Research Advisory Committee

Rationale & Draft Concept for Coordinated Clinical Research Networks

Bethesda, Maryland

August 17, 2004

Agenda

- Review of FY06 Clinical Research Network Concepts
  - DAIDS response to input
  - Discussion and review
  - Balloting
- Center for HIV/AIDS Vaccine Immunology (CHAVI)
  - Discussion and review
  - Balloting

Leadership for HIV and AIDS Clinical Trials Networks

- **Objectives:**
  - Establish cooperative clinical trials groups
- **Mechanism:** U01
- **Expansion/Renewal:** New
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Sites For HIV Vaccine, Prevention and Therapeutic Clinical Trials

Site RFA

- **Objectives:**
  - Establish clinical trial units as components of one or more clinical trials networks
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Leadership Groups RFA

- Translational Research / Drug Development
- Mother to Child Transmission
- Microbicides
- HIV Vaccines
- Prevention of HIV Infection
- Optimization of Clinical Management including Co-Morbidities

Populations

HIV Vaccines

- Identify a safe and effective world wide vaccine, e.g. all clades, exposures, HLA, etc)
- Determine correlate(s) of protection
- Develop cohorts to conduct all phases of clinical trials
- Develop new assays to measure full breadth of induced immune response
- Standardize and optimize trial designs
- Make specimens available to others

Mother to Child Transmission (MTCT)

- Continue to identify safe, practical, and effective approaches to further reduce MTCT
- Interruption of transmission through breast feeding
- Evaluate safety and PK of new drugs, drug combinations in pregnancy and newborns
- Safety and efficacy of vaccines to prevent MTCT and BF transmission
- Safety and efficacy of passive immunization
- Establish long term follow-up of newborns

Microbicides

- Identify a microbicide that is very safe and effective
- Determine correlates of short and long term safety
- Evaluate and optimize acceptability and adherence
- Evaluate user and partner acceptability and adherence

Translational Research / Drug Development

- Evaluate ART aimed at novel mechanisms of action/new targets, e.g. viral evolution, host response, elimination of viral reservoirs and co-factors which influence response to therapy and complement and expand research being done by industry
- Evaluate evolving therapies for patients with co-infections
- Conduct pharmacokinetic studies in children and adolescents to enable licensure and optimize use
- Integrate immune-based therapies in treatment regimens, (antiviral effect and immune reconstitution)

Optimization of Clinical Mgmt, including Co-Morbidities

- Optimize therapies for safety, adherence, resistance, durability of response and prevention of transmission
- Evaluate effectiveness of new regimens, e.g. those using agents with novel mechanisms of action
- Concurrent evaluation of ARV and other therapeutic modalities to manage co-morbidities and co-infections
- Better ways to use available agents, e.g. comparison of dosing regimens, timing of ARV therapy (with our without TB therapy), impact of traditional medicines on response to therapy
- AIDS related malignancies, metabolic side effects
- Other complications of ARV therapy and/or progressive HIV infection

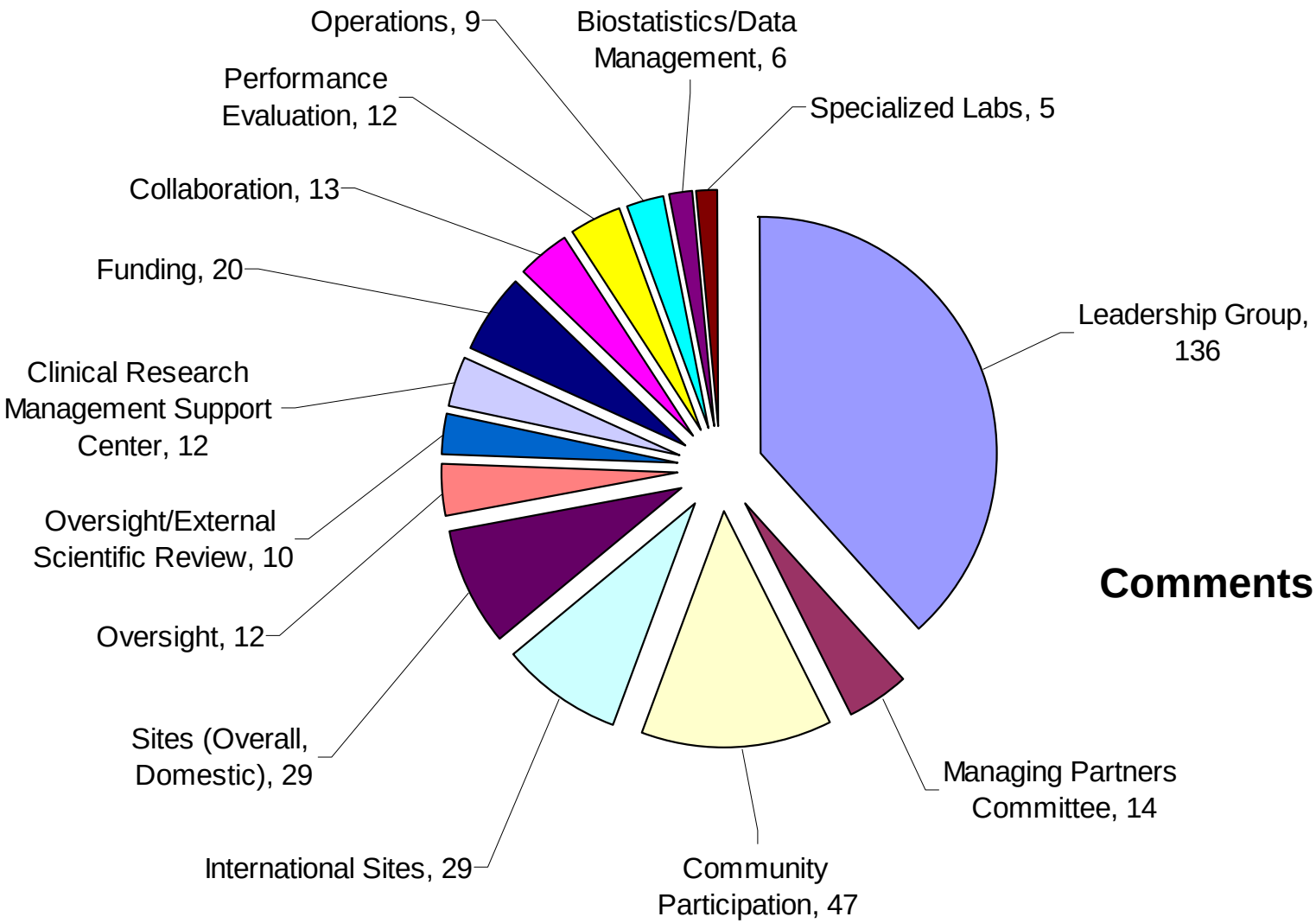
Prevention of HIV Infection

- Identify more practical, safe and effective approaches to halt the spread of HIV
- Evaluate worldwide suitability and sustainability of those approaches
- ART to prevent transmission
  - Acute/early infection
  - Established infection
  - PEP and PREP
- Treatment or prevention of STIs
- Behavior interventions to reduce HIV risk behaviors AND acquisition or transmission
- Interventions to reduce HIV acquisition or transmission in drug users

How Did We Solicit Input?

- Individual consultations
- Group meetings
- Network leadership meetings
- Inter-IC meetings
- Community meetings
- Public comments through website
- Open meeting sponsored by OAR
- ARAC meetings

Input By Comment Category



Comments Received: 354
Sources: 38

Response to ARAC & OAR WG

Comments

ARAC #1: Optimal Strategies for Balancing Fixed Infrastructure Costs, Incremental Per Protocol Costs, and Variable per Case Costs

OAR WG #9: DAIDS clinical research funding should support appropriate levels of infrastructure and provide DAIDS-controlled incentives to support the direct costs for the conduct of clinical trials

Impact on Concept & Actions

DAIDS will clarify language in both concepts to define the basis of site funding

RFAs will provide guidance for constructing ‘core’ budgets to support basic clinical trials capacity

Sites receive incremental protocol costs from networks

DAIDS will work with networks to harmonize site evaluation processes

Primary responsibility for site evaluation to remain with networks

Response to ARAC & OAR WG

Comments

ARAC #2: Minimizing Unnecessary Redundancy in the Support Cores

OAR WG #7a: Duplication of network core resources should be minimized wherever possible by use of common resources

OAR WG #7b: Avoidance of redundancy in network missions is desirable

Impact on Concept & Actions

RFAs to require coordinated use of network resources

LG applicants required to describe interactions with other NIAID/NIH-sponsored HIV/AIDS networks

Pre-award review of Managing Partners Committee inter-network coordination plan

DAIDS to support inter-network coordination through Clinical Research Management Support Contract

Response to ARAC & OAR WG

Comments

ARAC #3: Criteria for Evaluation

Impact on Concept & Actions

Evaluation criteria shall define priorities, goals and objectives and clarify areas of emphasis

Specific criteria for each scientific priority area

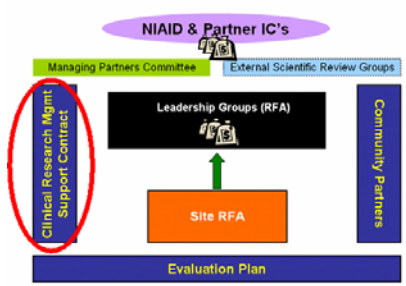
Peer-review groups constituted with expertise to assess applications

Selection criteria for network funding addressing comprehensive scientific priorities

Response to ARAC & OAR WG

Comments

ARAC #4: Clinical Management Support Contract



Impact on Concept & Actions

Staffing plan for cross-DAIDS team to manage contract based on analysis of anticipated contract activities, staff expertise and workload impact

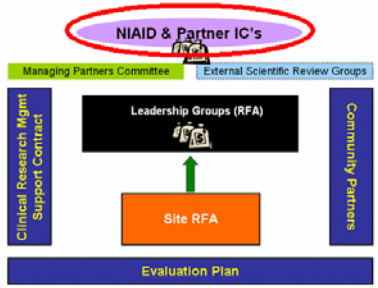
Response to ARAC & OAR WG

Comments

ARAC #5: Effective Partnerships at NIH

OAR WG #6: To provide better coordination and efficiency and avoid redundancy, strong incentives should be given for intra-country communications and collaboration between all similar resources

Promotion of local or in-country scientific and administrative leadership, ownership and investment in the research enterprise could also promote improved coordination and efficiency



Impact on Concept & Actions

DAIDS has engaged NIAID Divisions and NIH ICs to identify collaborative research opportunities and obtain funding commitments

IC-specific priorities incorporated into scientific priority areas of developing RFAs; ongoing process

Roles of IC partners in network governance commensurate with commitment and responsibilities

Response to ARAC & OAR WG

Comments

ARAC #6: Effective Partnerships with Other Agencies

OAR WG #6: To provide better coordination and efficiency and avoid redundancy, strong incentives should be given for intra-country communications and collaboration between all similar resources

Promotion of local or in-country scientific and administrative leadership, ownership and investment in the research enterprise could also promote improved coordination and efficiency

Impact on Concept & Actions

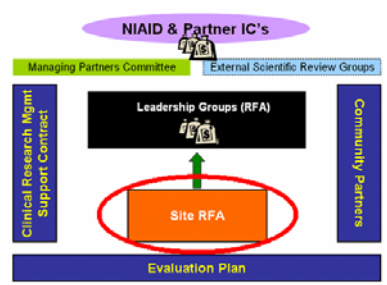
Linkages developed with US Government agencies (e.g. DOD, CDC, State, USAID & HRSA) to maximize opportunities

Collaborations with EDCTP, MRC, ANRS, World Bank, BMGF, FNIH, a variety of NGO's, and other organizations to leverage complementary strengths and shared interests

Response to ARAC & OAR WG

Comments

ARAC #7: Role of Major Interdisciplinary Centers vs. Smaller Clinical Sites



Impact on Concept & Actions

Flexible application/funding options for small clinical sites clarified in site RFA

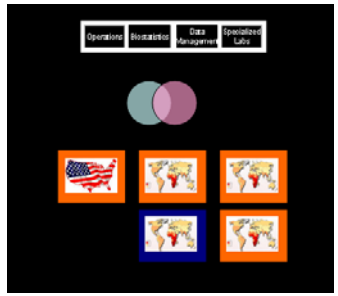
DAIDS will conduct pre-application meetings worldwide including resource poor settings domestically and internationally

DAIDS will produce and distribute information and guidance to prospective applicants

Response to ARAC & OAR WG

Comments

ARAC #8: Clinical and Basic Science Research vs. Clinical Trials Research



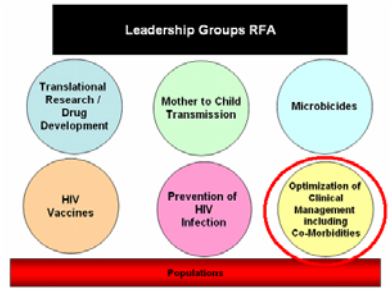
Impact on Concept & Actions

DAIDS will include language in the RFA to indicate that basic research is not a scientific priority and will not be directly supported through the network programs

Response to ARAC & OAR WG

Comments

ARAC #9: Definition of "Optimizing Clinical Management"



Impact on Concept & Actions

To clarify intent DAIDS has changed title of the priority area to: "Optimization of Clinical Management, Including Co-Morbidities"

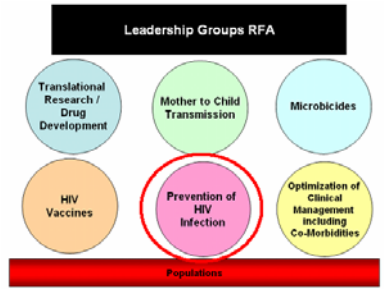
RFA to provide detailed examples of research that distinguish this area from more traditional 'drug development' and clarify relationship to "operational research"

Response to ARAC & OAR WG

Comments

ARAC # 10: Prevention Research

OAR WG #2: DAIDS scientific priorities for AIDS clinical research in the areas of therapeutics, vaccines, and prevention should be more clearly defined now, be integrated with and reflect the priorities and plans of other NIH HIV/AIDS research endeavors, and be reassessed annually



Impact on Concept & Actions

RFAs to define and provide examples for each priority area of research, including those aspects of prevention research with are outside of HIV vaccines, mother-to-child transmission, and microbicides (e.g. STI treatment, ARVs, male circumcision research, behavioral research).

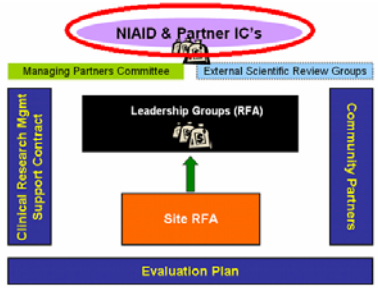
DAIDS will continue ongoing efforts to collaborate with NIH ICs with complementary strengths (e.g. behavioral research, special populations)

Response to ARAC & OAR WG

Comments

ARAC #11: Highest Priority Science Should Drive the Structure (i.e., Infrastructure) of the NIAID Clinical Trials Endeavor, rather than vice versa

OAR WG #1: The highest priority science must drive the structure of NIAID's clinical trials endeavor, rather than vice versa



Impact on Concept & Actions

DAIDS will ensure that networks address the highest priority research questions that are well-suited to investigation in that setting

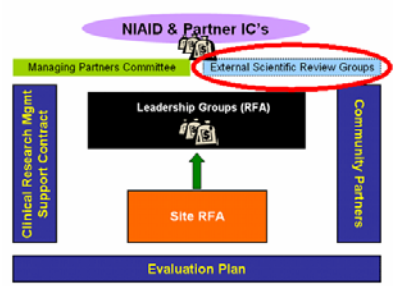
DAIDS will remain receptive and responsive to suggestions for use of 'non-network' mechanisms to address research under-represented or not optimally-suited for study in networks

Response to ARAC & OAR WG

Comments

ARAC #12: Annual Reassessment of Scientific Priorities for Clinical Trial Research
ARAC #13: Regular External Evaluation of Network Progress
ARAC #14: Objective External Review and Approval of Major (e.g., Expensive) Clinical Trials

OAR WG #3a: Objective external review of major clinical trials should be routine
OAR WG #3b: Regular external evaluation of the progress of the standing networks should be conducted and that oversight should be integrated into network operations



Impact on Concept & Actions

DAIDS and ARAC to determine best approach to objective external review of scientific priorities for clinical trial research

DAIDS and ARAC to determine best approach to objective review of major clinical trials

Response to ARAC & OAR WG

Comments

ARAC #15: Streamlining Protocol Development

OAR Working #5: Protocol development and implementation must be streamlined and be appropriate for the science being conducted

Impact on Concept & Actions

RFAs to emphasize need for efficiency in protocol development

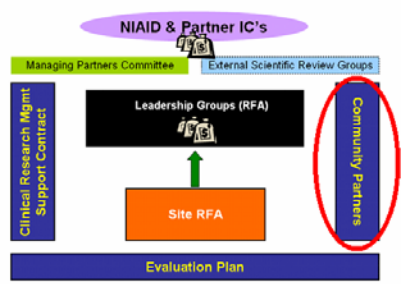
Protocol development procedures and management included in review criteria

DAIDS to invoke industry-based (or other relevant) standards of performance

Response to ARAC & OAR WG

Comments

OAR WG #4: Community involvement and participation must be routinely incorporated into all components of DAIDS-supported clinical research and supported through specific mechanisms with investment of resources



Impact on Concept & Actions

Requirement for inclusion of community input at all levels to be strongly represented in the RFAs

Ongoing discussions between DAIDS, community representatives, community advisory boards, and current network leadership to identify issues and formulate role, membership and structure of Community Partners Committee

Response to ARAC & OAR WG

Comments

OAR WG #8: Training and capacity building that promotes local or in-country ownership/investment in the research enterprise must accompany research support for sites in both U.S. and international resource-poor settings

Impact on Concept & Actions

DAIDS has merged the Domestic and International Site concepts, into a single Clinical Site concept
NIAID will design and incorporate suitable review criteria and peer-review committees to review applications

Managing Partners Committee to provide strategic leadership in training and capacity-building, and efficient use of resources across networks

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Discussion and Review